57. The aerosol composition of claim 23, wherein the nanoparticulate drug particles have an effective average particle size of less than about 100 nm.

58. The aerosol composition of claim 23, wherein the nanoparticulate drug particles have an effective average particle size of less than about 50 nm.

REMARKS

Applicants respectfully request reconsideration of this application.

I. STATUS OF THE CLAIMS

Following entry of this amendment, claims 11-38, 40-45, and 46-58 are pending. Claims 1-10, 39, and 46, were cancelled, without prejudice or disclaimer thereof, and claims 11, 15, 18-23, 26, 29-33, 35, 37, 40, 42, 43, and 44 were amended. Claims 11, 23, 35, 37, 40, 42, 43, and 44 were amended to recite an aggregate particle size of less than or equal to about 100 microns in diameter. Support for this amendment can be found in the specification at, for example, page 13, lines 26-28; and page 21, lines 1-4, of the specification. Claims 18-22 and 29-33 were amended to replace the abbreviation "MMAD" with the phrase "mass median aerodynamic diameter." This abbreviation is well known in the art. *See e.g.*, page 144 of P. Byron, "Aerosol Formulation, Generation, and Delivery Using NonMetered Systems," *Respiratory Drug Delivery*, 144-151, 144 (CRC Press, 1989) (EXHIBIT 1). Claims 15 and 26 were amended to delete the Markush group and to recite one particle size for the composition. New claims 51-54 and 55-58 recite the particle sizes cancelled from original claims 15 and 26, respectively.

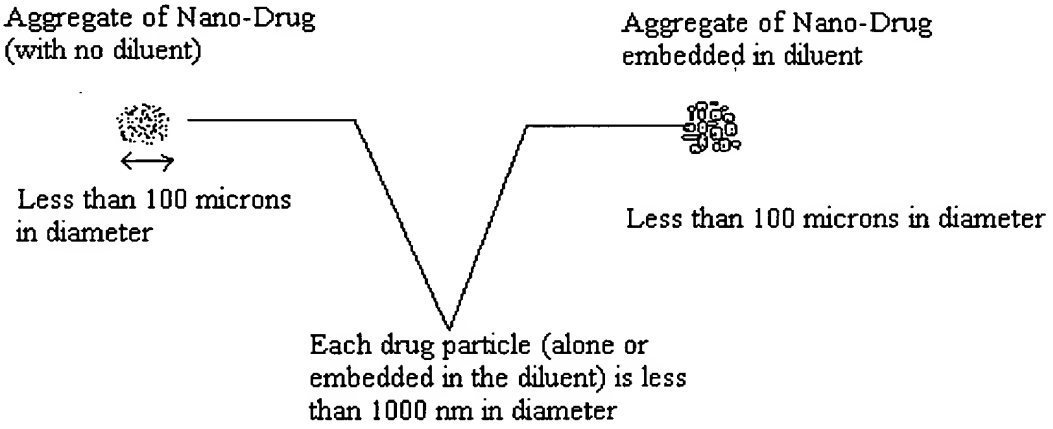
Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. SUMMARY OF THE INVENTION

The claimed invention is directed to dry powder aerosols of nanoparticulate compositions for pulmonary and nasal delivery. Essentially every inhaled particle of the aerosols contains at least one **nanoparticulate** drug particle. This is not shown or suggested

by the cited prior art. Non-aerosol preparations of submicron sized water-insoluble drugs are described in U.S. Patent No. 5,145,684.

Dry powder aerosols according to the invention do not consist of liquid droplets. Rather, they consist of aggregates of nanoparticulate drug, or aggregates of diluent comprising embedded nanoparticulate drug. The size of the dry powder aggregates determines where they will be deposited in the respiratory tract (and not the particle size of the drug comprised within the aggregates). The dry powder aerosols of the invention are graphically depicted below.



The ***improvement*** the invention provides over prior art aerosol compositions is the discovery that **nanoparticulate drugs** can be effectively employed in dry powder aerosol formulations. The aerosols comprising nanoparticulate drug provide superior properties as compared to aerosols comprising micronized drugs.

For example, the nanoparticulate size of the active agent results in an increase in the number of drug particles per unit dose, thereby producing a distribution of the nanoparticulate drug particles over a larger physiological surface area as compared to the same quantity of delivered micronized drug. This results in more favorable drug delivery profiles, such as a more complete absorption and rapid onset of action. *See e.g.*, page 22, lines 17-22, of the application.

The present invention also enables the aerosol delivery of high doses of drug in an extremely short time period, *i.e.*, 1-2 seconds (1 puff). This is in contrast to the conventional

4-20 min. administration period observed with pulmonary aerosol formulations of micronized drug. *See* page 23, lines 7-10, of the application.

Furthermore, the dry aerosol nanoparticulate powders of the present invention are spherical and can be made smaller than micronized material, thereby producing aerosol compositions having better flow and dispersion properties, and capable of being delivered to the deep lung. *See* page 23, lines 11-14, of the application.

Finally, the aerosol compositions of the present invention enable rapid nasal delivery. Nasal delivery of such aerosol compositions are absorbed more rapidly and completely than micronized aerosol compositions before being cleared by the mucociliary mechanism. *See* page 23, lines 15-18, of the application.

III. OFFICE ACTION

A. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1-50 were rejected under 35 U.S.C. § 112, first paragraph, as being allegedly based upon a disclosure which is not enabling. Office Action at page 2. Applicants respectfully traverse this ground for rejection.

1. The Examiner Alleged that the Particle Size of the Drug and the Identity of the Drug Are Critical to the Invention but not Enabled by the Disclosure

In support of this ground for rejection, the Examiner stated that "[t]he independent composition claims (claims 1, 11, 23, 35, and 37) teach several different aerosol compositions. However, the required medicament and its particle size, critical or essential to the practice of the invention, but not included in the claim(s) are not enabled by the disclosure." Office Action at page 2. Applicants courteously disagree with the Examiner's analysis and conclusion.

In addition, the Examiner asserted that independent method claims 39, 40, and 42-44 teach a variety of well-known aerosol techniques, and that applicant allegedly does not disclose any improvement on these known methods.

2. Applicants' Claims, As Amended, Recite an Aggregate Particle Size as well as the Particle Size of the Active Agent Contained Within the Aggregate Particle

While Applicants respectfully disagree with this ground for rejection, independent claims 11, 23, 35, 37, 40, 42, 43, and 44 have been amended to recite an aggregate particle size of less than or equal to about 100 microns in diameter. Support for this amendment can be found in the specification at, for example, page 13, lines 26-28; and page 21, lines 1-4, of the specification. The aggregate particle comprises nanoparticulate drug having a particle size of less than about 1000 nm, as depicted graphically above.

In contrast to the Examiner's assertion, the aerosols of the invention are not dependent upon the specific active agent contained within the aerosol. The benefits of the compositions of the invention are dependent upon: **(1) the size of the aggregate particles forming the aerosol and (2) the particle size of the active agent contained within the aggregate particle**. Because these two particle sizes are specified in the independent claims, Applicants claims are enabled. As such, withdrawal of this ground for rejection is respectfully requested.

3. Applicants' Method Claims Are Directed to Dry Powder Aerosols of Nanoparticulate Active Agents, Which Are Not Shown or Suggested in the Prior Art

As noted above in the Summary of the invention, the claimed invention is directed to dry powder aerosols of **nanoparticulate** compositions for pulmonary and nasal delivery. Such compositions, and methods of making and using such compositions, were not known prior to the present invention. Accordingly, Applicants' claimed invention provides an improvement over the prior art, an improvement which is enabled by the disclosure of the invention. Withdrawal of this ground for rejection is respectfully requested.

B. Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 6-10, 18-22, and 29-33 were rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly

claim the subject matter which Applicants regard as the invention. Office Action at page 3. Applicants respectfully traverse this ground for rejection.

In support of this ground for rejection, the Examiner stated that Applicants failed to "define the term 'MMAD' in either the claims or the specification." Office Action at page 3. Claims 6-10, 18-22, and 29-33 were amended to replace the abbreviation "MMAD" with the phrase "mass median aerodynamic diameter." This abbreviation is well known in the art. *See e.g.*, page 144 of P. Byron, "Aerosol Formulation, Generation, and Delivery Using NonMetered Systems," *Respiratory Drug Delivery*, 144-151, 144 (CRC Press, 1989) (EXHIBIT 1).

Because Applicants claims are definite, withdrawal of this ground for rejection is courteously requested.

C. Rejection of the Claims Under 35 U.S.C. § 102(e)

Claims 1-5, 39, and 46 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Wiedmann et al., U.S. Patent No. 5,747,001. Office Action at page 3. Applicants respectfully traverse this ground for rejection.

While Applicants respectfully disagree with this ground for rejection, claims 1-5, 39, and 46 have been cancelled for the sole purpose of advancing the prosecution of this case. Applicants reserve the right to prosecute the subject matter of the cancelled claims in this or another application.

As this ground for rejection is moot, withdrawal thereof by the Examiner is courteously requested.

D. Rejection of the Claims Under 35 U.S.C. § 103(a)

Claims 1-22, 35-43, 46, 47, 49, and 50 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Chapter 13 of Aerosols in Medicine. Principles, Diagnosis and Therapy (Elsevier Science Publishers, 1993) ("Aerosols"). Office Action at page 4. Applicants respectfully traverse this ground for rejection.

Claims 1- 50 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Aerosols, as applied to claims 1-22, 35-43, 46, 47, 49, and 50, above, and further in view of

Remington's Pharmaceutical Sciences (Mack Publishing Co., 1990) ("Remington's"). Office Action at page 5. Applicants respectfully traverse this ground for rejection.

1. Examiner's Basis for the Rejections

In support of these grounds for rejection the Examiner stated that Aerosols teaches that "for penetration into lower airways, it is generally accepted that the majority of particles should be smaller than 5 μm in diameter . . . [and] that this size can be achieved either by treating the substance in a ball mill or by micronizing in a jet mill." Office Action at page 5.

Continuing, the Examiner stated that Remington's is cited as it teaches the use of lyophilization. Office Action at page 5.

2. The Cited References Do Not Teach or Suggest Aerosols Comprising Nanoparticulate Active Agents

The cited references **do not** teach aerosols comprising nanoparticulate active agents. Applicants discovered and patented in U.S. Patent No. 5,145,684 ("the '684 patent") that stable nanoparticulate compositions can be made employing at least one surface stabilizer for the active agent. The surface stabilizer acts as a steric hindrance to particle aggregation, thus preventing particle size growth of the active agent. This is graphically demonstrated in EXHIBIT 2, which showed nanoparticulate drug having a surface stabilizer adsorbed onto the surface of the drug.

The present invention is an improvement over the teachings of the '684 patent, as it has now been discovered that such stable nanoparticulate compositions can be effectively employed in dry powder aerosols. Aerosols comprising such stable nanoparticulate compositions are **not** taught or suggested by Aerosols or Remington's.

While prior art teaches desirable droplet sizes for administration of drug, the references do not teach how to incorporate drug into such droplet or aggregate particle sizes. It is this problem that Applicants' claimed invention addresses and solves: how to effectively administer an active agent in a dry powder aerosol dosage form.

This is significant in that the aerosols of the present invention exhibit significant advantages over aerosols of the prior art, such as those taught by Aerosols and Remington's. For example, because of the nanoparticulate size of the active agent of the claimed invention, the claimed aerosols exhibit a more favorable drug delivery profile, such as a more complete

absorption and rapid onset of action. Furthermore, the aerosols of the present invention enable the aerosol delivery of high doses of drug in an extremely short time period, *i.e.*, 1-2 seconds (1 puff), which is in contrast to the conventional 4-20 min. administration period observed with pulmonary aerosol formulations of micronized drug. *See* page 23, lines 7-10, of the application. In addition, the dry powder nanoparticulate aerosols of the claimed invention are spherical and can be made smaller than micronized material, thereby producing aerosol compositions having better flow and dispersion properties, and capable of being delivered to the deep lung. *See* page 23, lines 11-14, of the application.

Accordingly, because the claimed invention is not taught or suggested by Aerosols or Remington's, and because the claimed invention provides dramatically superior benefits over prior art compositions and methods, withdrawal of this ground for rejection is respectfully requested.

IV. CONCLUSION

Applicants respectfully request reconsideration of this application in view of the above amendments and remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

Should the Examiner have any questions or comments regarding the pending application or this Amendment, the Examiner is requested to call the undersigned at 202-672-5538.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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